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Michelle P. Chicos — Michelle P. Chicos

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Frederick M. Ausubel et al.	Art Unit:	1641
Serial No.:	08/962,750	Examiner:	R. Swartz
Filed:	November 3, 1997		
Title:	METHODS OF SCREENING COMPOUNDS USEFUL FOR PREVENTION OF INFECTION OR PATHOGENICITY		

BOX APPEAL
Assistant Commissioner For Patents
Washington, DC 20231

APPELLANTS' BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 CFR § 1.192

In support of appellants' notice of appeal filed April 14, 2000 of the Examiner's final rejection mailed October 14, 1999, submitted herewith in triplicate is appellants' brief on appeal.

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TABLE OF CASES

Real Party in Interest

The real parties in interest in this case are the above-captioned appellants, as well as appellants' assignees, the General Hospital Corporation and the Netherlands Cancer Institute.

Related Appeals and Interferences

The parent application to this case, U.S. Serial No. 08/411,560, is presently on appeal. There are no currently pending interferences related to this application.

Status of Claims

Claims 1-24, 26, and 28-30 are currently pending.

Claims 25, 27, and 31-45 have been canceled.

Claims 1-24, 26, and 28-30 were finally rejected in the Final Office Action mailed on October 14, 1999 and are appealed.

Status of Amendments

Appellants' amendment filed with their Reply of July 21, 1999 has been entered. The amendment filed concurrently with the Notice of Appeal on April 14, 2000 was not entered.

A Supplemental Amendment that limits the issues on appeal is filed

herewith. For the reasons explained below, appellants request entry of this amendment and consideration of the appeal based on the claims in Appendix B. Alternatively, if the amendment is not entered, appellants' appeal is based on the claims as they presently stand in this case, which are found in Appendix A.

Summary of the Invention

In general, appellants' claimed invention features drug discovery screening methods involving exposing two different eukaryotic organisms, one of which is not a rodent, to the same pathogen in the presence of a compound and detecting inhibition or reduction of pathogenicity of the pathogen in each of the organisms. This invention is based on appellants' discovery that pathogens utilize the same virulence genes to trigger disease in evolutionarily disparate hosts such as mice, nematodes, and plants. Appellants' discovery therefore provides for new screening methods to identify anti-pathogenic therapeutics that combat microbial infection and disease.

Issue

The sole issue on appeal is whether the Examiner erred in rejecting claims 1-24, 26, and 28-30 as obvious under 35 U.S.C. § 103(a).

Grouping of Claims

For the purpose of this appeal, the claims are grouped as follows: Group I (claims 1-5); Group II (claim 6 and claims dependent thereon), Group III (claim 7 and claims dependent thereon); Group IV (claim 12); Group V (claim 13); Group VI (claim 14); Group VII (claim 15); Group VIII (claims 20 and 21); Group IX (claim 22-24, 26, and 28); and Group X (claims 29-30).

Case History

In consideration of the Examiner's position and to clarify the history of prosecution, appellants summarize below the obviousness rejections and appellants' responses to those rejections. A more detailed discussion of the issues raised in the final Office Action and Advisory Action is presented below.

A) The patent application was filed November 3, 1997 and assigned U.S.S.N. 08/962,750. This application is a continuation-in-part of U.S.S.N. 08/852,927, filed May 8, 1997, which is a continuation-in part of U.S.S.N. 08/411,560 filed March 28, 1995. Due to a restriction requirement election, claims 1-30, drawn to a method of identifying compounds which inhibit pathogens, were pursued. Claims 31-45 were later canceled.

B) In the first Office Action mailed January 21, 1999, claims 1-30 were rejected, under 35 U.S.C. § 103(a), as being unpatentable over Elrod et al. (*J. Bacteriol.* 46:633-645, 1942; "Elrod") or Schroth et al. (*Pseudomonas aeruginosa: Ecological Aspects and Patient Colonization*, pp. 1-29, 1977; "Schroth") in view of Kominos et al. (*Appl. Microbiol.* 24(4): 567-570, 1972; "Kominos") and further in view of Geels (*J. Appl. Bacteriol.* 79: 38-42, 1995; "Geels") and Conrad et al. (*Rev. Inf. Dis.* 13: S364-369, 1991; "Conrad").

C) In response to the prior art rejections raised in the first Office Action, appellants' argued that none of the references of record taught or suggested that compounds might be identified that inhibited or reduced the pathogenicity of a single pathogen using methods involving at least two different eukaryotic organisms, let alone identifying compounds that inhibited or reduced the pathogenicity of such a pathogen using a combination of nematode and plant assay systems.

Appellants noted that the opposite teaching was found in the Elrod reference, and that Elrod plainly taught away from appellants' discovery of common virulence factors, suggesting instead that pathogenicity in different organisms requires different factors. Appellants further noted that the Elrod, Schroth, Kominos, Conrad, and Geels references, alone or in combination, did not teach or suggest any screening methods employing two different eukaryotic organisms to identify compounds that inhibited or

reduced the pathogenicity of the same pathogen.

Appellants also pointed out that no evidence made of record in the case indicated that, at the time of appellants' invention, one skilled in the art would have recognized that evolutionarily diverse organisms, such as plants and animals, might be used together to develop assays for screening candidate compounds for anti-pathogenic activity. Appellants further pointed out that no analysis of the cited publications was presented in the Office Action that explained what specific understanding, theory, or technical principle found in these references would have suggested a combination leading to appellants' claimed screening methods. Appellants' argued that their technical breakthrough demonstrating the existence of common virulence factors used by pathogens to infect multiple hosts was nowhere taught or suggested by the cited publications. Moreover, appellants noted that the obviousness rejection hinged essentially on some observations about *Pseudomonas* pathogenicity — one of which was over fifty years old — that provided no reasonable scientific basis or rationale for developing appellants' claimed methods.

D) A final Office Action in this case was mailed October 14, 1999. In this Office Action the Examiner maintained the obviousness rejection, asserting that appellants argument "concerning recognition of whether the pathogenicity in plants and animals is due to common or different virulence factors is directed to a criticality not

claimed." In addition, the Examiner stated:

> The cited references teach that *Pseudomonas* is a pathogen frequently involved in disease in both plants and animals. Because of this, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to test drug efficacy of a variety of suspected compounds for controlling or eradicating the presence of *Pseudomonas* in both plants and animals. In addition, it would have been obvious to utilize models of both plants and animals in order to identify such compounds.

E) In response, appellants filed an Amendment on April 14, 2000. Appellants amended the claims to focus the claimed invention on the "common virulence factor" concept. As amended, the claims were directed to cover appellants' technical breakthrough demonstrating the existence of common virulence factors that are used by pathogens to infect multiple hosts.

F) A Notice of Appeal was filed on April 14, 2000.

G) An Advisory Action was mailed on May 30, 2000. In this Action, the Examiner declined to enter appellants' amendment of April 14, 2000 on the asserted ground that the proposed amendment raised new issues that would require further consideration and/or search. In particular, the Examiner stated:

> [T]he amendment raises new issues of how to distinguish between compounds which inhibit or reduce pathogenicity by

affecting the function of a common virulence factor versus affecting the function of multiple virulence factors. There are no methods [sic] steps for making such distinction.

ARGUMENT

As is clear from the prosecution history above, the pending claims stand rejected under 35 U.S.C. § 103. The bases for this rejection, as applied in the Final Office Action and Advisory Action, and appellants' response to this rejection are presented below.

Rejection under 35 U.S.C. § 103(a)

Claims 1-24, 26, and 28-30 stand rejected under § 103(a) in view of several references presently made of record in this case. For the following reasons, this rejection, as applied to the claims found in either Appendix A or B, should be withdrawn.

The test of obviousness *vel non* is statutory. It requires that one compare the claim's "subject matter as a whole" with the prior art "to which said subject matter pertains." 35 U.S.C. §103(a). The inquiry is fact-specific. This is so "whether the invention be a process for making or a process of using, or some other process." *In re Kuehl*, 475 F.2d 658, 665, 177 U.S.P.Q. 250, 255 (C.C.P.A. 1973). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *In re Fine*, 837 F.2d 1071,1075, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). To prevent the use of

hindsight based on the invention to defeat patentability, the Federal Circuit requires the Examiner to show a motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). The Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *Id.* When the references cited by the Patent Office fail to establish a *prima facie* case of obviousness, the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d at 1074, 5 U.S.P.Q.2d at 1598.

In the present case, the Examiner concludes that it was obvious at the time the invention was made to test drug efficacy of a variety of suspected compounds for controlling or eradicating the presence of *Pseudomonas* in both plants and animals. In drawing this conclusion, the Examiner relies entirely on anecdotal evidence found in the references of record: In short, the Examiner asserts that, since *Pseudomonas* lives on plant and animal hosts, it is obvious to screen for drugs using both hosts. But nowhere does the Examiner identify any scientific principal or theory found in the references to suggest the claimed invention. In fact, as explained in more detail below, none of the references of record mentions using two different eukaryotic organisms together for screening therapeutics that inhibit or reduce pathogenicity of the same pathogen on different hosts, nor do the references provide any scientific rationale that would motivate

the skilled worker to conduct such screens.

Elrod

Looking first to the Elrod reference, appellants maintain that this reference does not teach or suggest that compounds may be identified that inhibit or reduce the pathogenicity of a single pathogen using methods involving at least two different eukaryotic organisms, let alone identifying compounds that inhibit or reduce the pathogenicity of such a pathogen using a combination of nematode and plant assay systems. Instead the opposite teaching is found in the Elrod reference. Although Elrod recognized that the pathogen, *Pseudomonas aeruginosa,* is capable of infecting both humans and plants, Elrod, unlike appellants, concluded that such dual pathogenicity resulted, not from the existence of common virulence factors found in the bacterium, but rather from the existence of different virulence factors, and possibly even from the existence of different strains of the same bacterium, each being responsible for causing infection in either a plant or a human. Evidence for this assertion is found, for example, at page 642 of the Elrod teaching, where the reference clearly states (emphasis added):

> It appears likely that the **phytotoxic [plant pathogenic] factors** of the organism [P. aeruginosa] **are not the same as the toxin substances that induce animal disease**. This was emphasized by the action of **rough variants** which, though not fatal to animals, retained their pathogenicity for plants.

Accordingly, there is clear evidence in the Elrod article of teaching away from the method claimed by appellants. Unlike appellants, who discovered that there are

common virulence factors needed to cause disease in plants and animals, Elrod teaches that "the phytotoxic factors of the organism are not the same as the toxic substances that induce animal disease." It follows then that Elrod teaches that different mechanisms are responsible for effecting disease in animal and plant hosts.

Moreover, Elrod fails to provide any reasonable predicate leading to appellants' claimed invention that utilizes two different hosts to identify compounds that inhibit or reduce pathogenicity of the same pathogen, and the Examiner has not provided any specific reasoning, in light of this teaching, as to why the invention was obvious to the skilled worker. If the toxic substances that cause disease in plants and animals are different, as explained by Elrod, then why would one skilled in the art use the two systems to screen for compounds that control or eradicate the presence of *Pseudomonas* in both plants and animals? In reality, given the Elrod teaching, skilled practitioners would not be motivated to employ plants and animal hosts together when screening for compounds to inhibit a pathogen, as the disease-causing mechanisms are taught to be different.

Schroth

With respect to the other primary reference, Schroth, the Office asserts that this reference teaches "that *Pseudomonas aeruginosa* infects patients in hospitals as well as agricultural plants." While appellants do not specifically disagree with this characterization of the Schroth reference, they point out that this reference, like Elrod,

provides no scientific basis for performing appellants' claimed methods. Schroth, like Elrod, fails to recognize that dual pathogenicity of *Pseudomonas* results from the existence of common virulence factors, and absent this recognition this reference is incapable of providing a logical basis for suggesting that effective inhibitory compounds for treating or preventing a pathogen infection in one eukaryotic organism might be identified by screening for those compounds in an entirely different eukaryotic organism.

Kominos

The Office uses Kominos only for teaching "that plants are an important source and vehicle by which *P. aeruginosa* colonizes the intestinal tract of patients, not for teaching any screening methods." Appellants again point out that this reference never teaches or suggests that a single pathogen possesses common virulence factors that render it pathogenic on multiple host organisms. Moreover, the finding that certain vegetables serve as a reservoir for *P. aeruginosa* provides no reasonable basis for concluding that screening methods might be developed to identify compounds that inhibit or reduce the pathogenicity of such a pathogen using methods involving two different organisms such as plants and animals, as presently claimed. Kominos does not even teach that *Pseudomonas* is a pathogen of plants.

Kominos, even when combined with Elrod and Schroth, does not teach or suggest appellants' discovery that common pathogenic virulence factors are involved in the infection of widely divergent animal species as well as plants, much less that

organisms such as nematodes and plants may be used together to identify compounds that inhibit or reduce the pathogenicity. Again, appellants point out that Kominos, like the other primary references, provides no insight into the disease-causing mechanism and absent such teaching provides no basis for appellants' screening methods.

Conrad

With respect to Conrad, the Office has stated that this reference is cited "as a method of testing a suspected compound for treatment of P. aeuriginosa infection in humans." Appellants note that Conrad does not suggest any aspect of the claimed invention, nor does it provide any motivation for its combination with the primary references. Conrad is singularly focused on determining the efficacy of one particular compound to treat *P. aeruginosa* skeletal infections in humans. Conrad never even mentions that screening systems apart from the described skeletal system might be used to evaluate the efficacy of the compound, aztreonam, against *Pseudomonas* pathogenicity. Morever, appellants note that Conrad, like all of the cited references, fails to recognize the existence of common pathogenic virulence factors that facilitate the claimed screening methods in multiple eukaryotic organisms designed to identify therapeutic agents useful for pathogen inhibition or reduction of pathogenicity.

Geels

Finally, with respect to Geels, the Office, relying on an apparently out-of-date definition found in Webster's that mushrooms are fungi and fungi are plants, has

stated that this reference teaches a "plant model testing a suspected compound for treatment of *Pseudomonas*." Appellants note that Geels teaches "*Pseudomonas tolaasii* control by kasugamycin in cultivated mushrooms (*Agaricus bisporus*)." It is appellants' understanding that mushrooms are classified in the kingdom Fungi, and plants are classified in the kingdom Planta. These organisms are therefore classified in distinct kingdoms and mushrooms are not plants. Accordingly, Geels does not teach a plant model to identify compounds that are efficacious for treating a plant pathogen.

Moreover, Geels also does not teach any method of using two different eukaryotic organisms to identify compounds that inhibit or reduce the pathogenicity of the same pathogen. Geels, like all of the other references of record, provides no logical basis, much less the motivation, for developing appellants' claimed methods.

The References Do Not Provide Appellants' Invention

In sum, despite the significant number of references cited, a *prima facie* case of obviousness has not been established in this case. None of the Elrod, Schroth, Kominos, Conrad, and Geels references is suggestive, alone or in combination, of the use or success of a drug screening system even remotely similar to the one disclosed and claimed by appellants. Indeed, if appellants' claimed invention was obvious in view of these references, someone should have at least suggested it in the fifty-three years between the publication of Elrod in 1942 and the filing of appellants' application in 1995, during which period researchers were searching diligently for new methods of identifying

drugs that combat microbial pathogenesis.

Differences between the prior art and the claimed invention are also apparent. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966)("[D]ifferences between the prior art and the claims at issue are to be ascertained.... Against this background, the obviousness or non-obviousness of the claimed invention is determined"). In particular, Elrod discusses different disease-causing mechanisms between plants and animals infected by *Pseudomonas*, while appellants teach that common virulence factors are capable of triggering disease in both. As none of the references provide any reasonable scientific basis for using two organisms together when screening for compounds that inhibit a pathogen, there can be no basis for combining these prior art references to produce the claimed invention.

Only through hindsight -- using the claimed invention as a roadmap -- is the Examiner able to arrive at the claimed invention. See *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985) ("It is impermissible to first ascertain factually what [appellants] did and then view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art"). To believe that one skilled in the art would be motivated to employ appellants' disclosed methods, especially when the only reference of record that discusses pathogen disease-causing mechanisms, Elrod, teaches away from appellants' claimed invention, is to assume a level of inspiration

constituting inventive activity. The contention that appellants' claimed screening methods are obvious is unsupported by the cited references, and the Office has not provided reasons as to why a skilled artisan, confronted with the same problem as the inventors, would select the elements from the cited references in the manner claimed.

Appellants submit that the cited references, either alone or in combination, do not render obvious the claims as found in either Appendix A or B. These references fail to teach, suggest, or motivate the use of compound screening methods employing at least two different eukaryotic organisms to identify compounds that inhibit or reduce pathogenicity of the same pathogen. The inventive screening methods resulted from appellants' crucial scientific discovery that common virulence factors existed, and not from the prior art. Accordingly, appellants respectfully request that the § 103 rejection in this case be withdrawn.

Additional Inventive Aspects of the Claims

Appellants further note that, with respect to the dependent claims, the references of record are even farther afield.

For example, none of the cited references specifically mention or suggest the use of the combination of a vertebrate and a plant (claim 5); a vertebrate and an invertebrate (claim 6); a plant and an invertebrate (claim 7); a plant and a plant (claim 12), a vertebrate and a vertebrate (claim 13), an invertebrate and an invertebrate (claim 14); or a nematode and a second eukaryotic organism (claim 9) in screens to identify

compounds that inhibit or reduce the pathogenicity of a single pathogen, nor do the references discuss or suggest appellants' claimed screening methods that exploit "fast killing" conditions (claims 20 and 29) as described in appellants' specification. Similarly, no reference of record teaches or suggests that the combination of an insect and a second eukaryotic organism (claim 15) may be used to identify compounds that inhibit or reduce the pathogenicity. Again, each of the references fails to recognize the existence of overlapping, common virulence factors that facilitate the particular screening methods of these claims, and no position to the contrary has been raised by the Office.

Entry of Amendment

Finally, appellants respectfully request entry of the Supplemental Amendment mailed concurrently with this appeal. This amendment, which, with respect to claims 1 and 22, is identical to that submitted by appellants with their reply of April 14, 2000, narrows the issues on appeal and expedites resolution of this case. This amendment raises no issues requiring a new search, as the Office's initial search is believed to have covered the common virulence factor concept embodied in appellants' claims as originally filed and as disclosed in appellants' specification. (See, for example, appellants' specification, at page 3, under the heading "Summary of Invention," where it is stated: "We have discovered that common pathogenic virulence factors are involved in infection and pathogenicity of both animal and plant hosts.") Similarly, the amendment does not raise any issue relating to the addition of new matter.

With respect to the statement made in the Advisory Action that there are no method steps for distinguishing between compounds which inhibit or reduce pathogenicity by affecting the function of a common virulence factor (versus affecting the function of multiple virulence factors), appellants respectfully point out that the amended claims do make this distinction. In particular, paragraph (b) of amended claims 1 and 22 requires identifying a compound that inhibits or reduces pathogenicity of the same pathogen in the two different hosts as a consequence of affecting the function of said common virulence factor in said same pathogen. Accordingly, it is appellants' position that this amendment does no more than narrow the issues on appeal, and on this basis request its entry.

Conclusion

Appellants respectfully request that the § 103 rejection of claims 1-24, 26, and 28-30 be reversed. A check for $310.00 is enclosed for the required appeal fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: October 16, 2000

Karen L. Elbing, Ph.D.
Reg. No. 35,238

James DeCamp, Ph.D.
Reg. No. 43,580

Clark & Elbing LLP
176 Federal Street
Boston, MA 02110-2214
Telephone: 617-428-0200
Facsimile: 617-428-7045

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Appendix A: Claims on Appeal

1. A method for identifying a compound which inhibits or reduces pathogenicity of the same pathogen in at least two different eukaryotic organisms said method comprising

(a) exposing said at least two different eukaryotic organisms, at least one of said organisms being a non-rodent, to said same pathogen in the presence of at least one candidate compound; and

(b) detecting inhibition or reduction of pathogenicity of said same pathogen as an indication that said candidate compound inhibits or reduces pathogenicity of said same pathogen in each of said eukaryotic organisms.

2. The method of claim 1, wherein said pathogen is a bacterium.

3. The method of claim 2, wherein said bacterium is *Pseudomonas aeruginosa*.

4. The method of claim 2, wherein said bacterium is *Pseudomonas aeruginosa* UCBPP-PA14.

5. The method of claim 1, wherein said eukaryotic organisms includes a vertebrate and a plant.

6. The method of claim 1, wherein said eukaryotic organism includes a vertebrate and an invertebrate.

7. The method of claim 1, wherein said eukaryotic organism includes a plant and an invertebrate.

8. The method of claim 5 or claim 6, wherein said vertebrate is a mammal.

9. The method of claim 6 or claim 7, wherein said invertebrate is a nematode.

10. The method of claim 9, wherein said nematode is a member of the genus *Caenorhabditis*.

11. The method of claim 5 or claim 7, wherein said plant is a member of the genus *Arabidopsis*.

12. The method of claim 1, wherein each of said eukaryotic organisms is a plant.

13. The method of claim 1, wherein each of said eukaryotic organisms is a vertebrate.

14. The method of claim 1, wherein each of said eukaryotic organisms is an invertebrate.

15. The method of claim 14, wherein said invertebrate is an insect.

16. The method of claim 15, wherein said insect is a lepidopteran.

17. The method of claim 16, wherein said lepidopteran is *Galleria* or *Plutella*.

18. The method of claim 14, wherein said insect is a dipteran.

19. The method of claim 19, wherein said dipteran is *Drosophila*.

20. The method of claim 1, wherein said method utilizes the nematode fast killing assay.

21. The method of claim 20, wherein said nematode fast killing assay involves the use of a *C. elegans* having a P-glycoprotein mutation.

22. A method for identifying a compound which inhibits or reduces pathogenicity of the same pathogen in a nematode and a plant, comprising

(a) exposing said nematode and said plant to said same pathogen in the presence of at least one candidate compound; and

(b) identifying a compound that inhibits or reduces pathogenicity of said same pathogen in said nematode and said plant.

23. The method of claim 22, wherein said pathogen is a bacterium.

24. The method of claim 23, wherein said bacterium is *Pseudomonas aeruginosa* UCBPP-PA14.

26. The method of claim 22, wherein said nematode is *Caenorhabditis elegans*.

28. The method of claim 22, wherein said plant is *Arabidopsis*.

29. The method of claim 22, wherein said method utilizes the nematode fast killing assay.

30. The method of claim 29, wherein said nematode fast killing assay involves the use of a *C. elegans* having a P-glycoprotein mutation.